UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,121	10/23/2000	Debra G. Gilbertson	00-53	2404

7590 01/31/2003

Gary E. Parker
ZymoGenetics, Inc.
1201 Eastlake Avenue East
Seattle, WA 98102

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/31/2003

(1)

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,121	GILBERTSON, DEBRA G.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11-13,15 and 17-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,11-13,15 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 11/13/02, as Paper No. 14. Claims 1-6, 9, 11-13, 15 and 17-25 are pending in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-6, 9, 11-13, 15 and 17-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41, 42, and 46-54 of copending Application No. 10/139,583 ('583, herafter). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '583 are drawn to methods of inhibiting zvegf3 activity in a mammal by administering a zvegf3 antagonist (claim 41), such as an antibody or antibody (claim 42), and methods of decreasing

zvegf3 activity in a mammal by administering an antibody specific for an epitope of zvegf3 (claims 46, 50) wherein the antibody can be a monoclonal antibody (claim 47, 51), a humanized antibody (claim 48, 52) or a single chain antibody (claim 49, 54). The antibodies used in claims 46-54 of '583 are specific for the same epitopes of zvegf3 as the antibody used in the methods of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 1-6, 9, 11-13, 15 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

6. A method for reducing zvegf3 activity in a mammal comprising administering to the mammal a composition comprising a zvegf3 antagonist in combination with a pharmaceutically acceptable delivery vehicle, in an amount sufficient to reduce zvegf3 activity, wherein said zvegf3 antagonist is an antibody that specifically binds to a dimeric protein having two polypeptide chains, wherein each of the polypeptide chains consists of a sequence of amino acid residues selected from the group set forth (see claim 1);

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to methods of reducing cell proliferation or extracellular matrix production in a mammal, methods of treating fibrosis in a mammal, and methods for reducing stellate cell reduction in a mammal using a zvegf3 antagonist wherein said zvegf3 antagonist is an antibody. The specification indicates that overexpression of Zvegf3 leads to stellate cell activation, extracellular matrix growth and increased cell proliferation (see p. 10, lines 12-20).

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods of reducing cell proliferation or extracellular matrix production in a mammal, methods of treating fibrosis in a mammal, and methods for reducing stellate cell reduction in a mammal using a zvegf3 antagonist wherein said zvegf3 antagonist is an antibody that specifically binds to a dimeric protein having two polypeptide chains wherein each of said polypeptide chains consists of a sequence of amino acid residues present in zvegf3 (specifically in the region of residues 230-345 of SEQ ID NO 2). The claims encompass methods of reducing or treating symptoms associated with mammalian disease or

disorder using an antibody. Therefore, the nature of the Invention is antibody treatment for mammalian disorders.

The breadth of the claims

The claims are very broad. For instance, the claims encompasses reducing cell proliferation or extracellular matrix production in a mammal, treating fibrosis in a mammal, and reducing stellate cell reduction in a mammal wherein the cell proliferation/extracellular matrix production, fibrosis and stellate cell activation is associated with a broad range of disease/disorders. Therefore, the claims encompass reducing cell proliferation associated with cancer (prostate carcinoma, see p.12 lines 27-34 of the specification), hepatitis, scleroderma, liver fibrosis, etc. (p. 10, lines34-p. 11 line 10)), treating fibrosis associated with diabetes, (p. 11, lines 21-35), pneumonia, hypertension, etc. (p. 12, lines 12-20) and reducing stellate activation associated with fibrotic disorders of the liver (see p. 11 lines 17-20). Therefore, the claims encompass treating a broad range of diseases/disorders associated with cell proliferation, extracellular matrix production and stellate cell activation.

The unpredictability of the art and the state of the prior art

As mentioned above, the claims encompass treating a wide range of mammalian disease/disorders associated with cell proliferation, extracellular matrix production and stellate cell activation by administering a zvegf3 antibody. In order for the treatment to be effective it is logical that zvegf3 activity must be essentially involved in the disease process. However, the relevant art recognizes that cell proliferative diseases such as cancer can be due to dominant genetic mutations which can function independent of other factors.

For instance, Kitamura (Mutation Research 2001; 477:165-171) teaches a gain-of function mutation of the c-kit receptor tyrosine kinase (KIT) that induces neoplasms of mast cells and interstitial cells of Cajal (ICCs) (see abstract). Kitamura indicates that c-kit encodes a receptor tyrosine kinase that is structurally similar to the receptors of platelet derived growth factor (PDGF) and vascular endothelial cell growth factor (VEGF) (see p. 165, second paragraph). Kitamura teaches that a gain-of-function mutant of KIT is activated in the absence of its ligand (see p. 167, first paragraph). Furthermore, Kitamura indicates that cells expressing the constitutively active gain-of-function mutant in the absence of ligand can develop into tumors in mice (See p. 167, second paragraph). Therefore, it is clear that dominant genetic mutations can lead to increased cell proliferation (and tumorigenesis), without the involvement of upstream factors (such as ligands). It is pointed out that Kitamura describes a cell proliferative disorder of interstitial cells. The claims encompass inhibiting or treating cell proliferative disorders of interstitial cells—and the specification discloses that Zvegf3 is structurally related to PDGF (and VEGF) and indicates that Zvegf3 binds to the PDGF receptor (see p. 4, lines 10-25). Therefore, the claims encompass inhibiting/treating the cell proliferation due to the mutation described by Kitamura. However, it is unlikely that the Zvegf3 antibody could inhibit/treat the cell proliferation due to the mutation described by Kitamura.

Regarding cell proliferative disorders of fibroblast cells, Dhanasekaran (Oncogene 1989; 17:1383-1394) that G proteins regulate several critical signaling pathways involved in cell proliferation, differentiation and apoptosis and several G proteins have been associated with mitogenic signaling in fibroblast cells (see abstract). Dhanasekaran teaches that G proteins are signal transduction proteins that provide signal coupling mechanisms to seven transmembrane

receptors inside the cell (see p. 1383, first paragraph). Dhanasekaran also indicates that there are a number of constitutively activated G protein mutants which result in increased cell proliferation and tumorigenesis (such as the gsp oncogene (p. 1385), the gip2 oncogene (p. 1386), Gα4 (p. 1387), and Gα12/13 (p.1388)). It is pointed out that the claims encompass methods of inhibiting/treating cell proliferative disorder of fibroblasts (see claim 2). However, there is no indication that zvegf3 is associated with the intracellular G-protein signal transduction. Therefore, without evidence to the contrary it is unlikely that the zvegf3 antibody could be used to inhibit/treat the cell proliferation due to the constitutively activated G proteins described by Dhanasekaran.

Regarding the activation of stellate cell activation, Mann (Gut 2002; 50:891-896) indicates that stellate cell activation is a complex process that is not yet fully understood and involves a number of different factors. Specifically, Mann teaches,

> "The hepatic stellate cell (HSC) is now well established as a key cellular element involved in the development of hepatic fibrosis and because of this there is considerable interest in establishing the molecular events that trigger and perpetuate HSC activation (see abstract)... HSC activation is a highly pleiotropic process that involves gross morphological, behavioral, and biochemical changes. These dramatic phenotypic changes require global reprogramming of HSC gene expression which in turn must be orchestrated by long term changes in the expression and/or activity of key transcriptional regulators of the HSC genome." (See p. 891, first column).

Mann indicates that there are a number of factors that are known to activate HSCs, such as NFκB, AP-1, Kruppel-like transcription factors, C/EBP, E-box transcription factors and c-Myb (see Mann p. 891-894). Mann also indicates "it will eventually be possible to map the major transcriptional pathways that result in HSC activation and thereby promote fibrosis. Future efforts should be particularly directed to in vivo studies with gene deleted mice or virus vector mediated delivery of dominant negative inhibitors to confirm a pathophysiological for these

potential orchestrators of HASC activation in the fibrogenic process." (See p. 895, last paragraph). Therefore, it is clear that a number of different factors are capable of activating stellate cells, even though the exact map has not been elucidated. Therefore, without evidence to the contrary, it is cannot be predicted that a zvegf3 antibody could inhibit stellate cell activation, because it is possible that the stellate cells could be activated by a factor independent of zvegf3.

Regarding the treatment of renal diseases, Yu (Current Opin. Pharm. 2002; 2:177-181) teaches that angiostatin II blockade is a standard anti-fibrotic therapy for renal diseases, but also indicates that it is unlikely that any single agent will effectively stop renal fibrosis. Specifically, Yu teaches,

> "Angiostatin II blockade has become a standard anti-fibrotic therapy in renal diseases because it slows progression to end-stage renal disease. However, current data support the notion that angiotensin II blockade alone cannot stop progressive fibrotic disease. Of an increasing number of therapies showing efficacy in animal studies, antibodies to transforming growth factor beta are the most thoroughly studied and are likely to be effective in human clinical trials. However, hints exist in the literature suggesting that no single agent will effectively halt renal fibrosis and that combinations of agents will be required." (See abstract, emphasis added).

Therefore, it is unlikely that that administration of zvegf3 antibody alone would be able to halt cell proliferation, extracellular matrix and stellate cell activation associated with fibrosis.

Working Examples and Guidance in the Specification

As mentioned in the previous Office Action, the specification has no working examples, whatsoever, demonstrating administration of a zvegf3 antibody to a mammal. There is no demonstration that treatment with the antibodies effectively reduces cell proliferation or extracellular matrix production, or effectively treats fibrosis or reduces stellate cell activation in

any mammal. The specification does indicate that overexpression of Zvegf3 leads to increased cell proliferation, increased extracellular matrix formation and stimulates production of TGF-B1 in stellate cells (an indication of stellate cell activation). However, the claims are very broad and encompass inhibiting cell proliferation by administration of a Zvegf3 antibody. Considering the relevant are recognizes mechanisms which could led to increased cell proliferation and extracellular matrix formation independent of Zvegf3 activity (see Kitamura and Dhanasekaran above), one of skill in the art could not predict that Zvegf3 antibody treatment would inhibit cell proliferation due to the constitutively active mutations described without additional experimentation.

Quantity of Experimentation

Considering the art teaches that there are cellular mechanism independent of zvegf3 activity (such as constitutively active mutants) which result in activation of cell proliferation, extracellular matrix production and stellate cell activation, one of skill in the art could not reasonably predict that the zvegf3 antibody could be used to treat any cell proliferative disorder without specific supporting evidence. Therefore additional experimentation is required in order to be able to reasonably predict which cells would respond to zvegf3 antibody treatment and which cells would not. The amount of additional experimentation required is considered to be undue because it would have to be shown that zvegf3 antibody could be used to inhibit any type of cell proliferation, extracellular matrix formation and stellate cell activation with a reasonable expectation of success. This would require testing the antibody in an extremely large number of different diseased cells in order to be able to reasonably predict that the zvegf3 antibody could be

used to inhibit any type of cellular proliferation (and extracellular matrix formation and stellate cell activation).

Level of the skill in the art

The level of the skill required is deemed to be high, considering the highly technical nature of the field.

Conclusion

Considering the high degree of unpredictability recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to use the claimed invention to the full scope encompassed by the broad claims is undue.

Response to Arguments

The previous Office Action set forth a rejection under 35 USC 112, first paragraph because the claims were not considered to be enabled for antibody therapy. Considering Applicants arguments and the submitted material to support applicants arguments, the rejection is withdrawn, because it does appear that antibody therapy for in vivo treatments is possible without undue additional experimentation.

However, the instant claims are still broadly written and encompass inhibiting/treating any type of cell proliferation, extracellular matrix formation and stellate cell activation. As mentioned above, the art recognizes that mechanisms exist and are used by diseased cells in order activate cell proliferation, extracellular matrix formation and stellate cell activation most

likely independent of zvegf3 activity. Therefore additional experimentation is required in order to be able to reasonably predict which diseased cells would respond to zvegf3 antibody treatment (see above). It is noted, however, that considering the claims are enabled for reducing zvegf3 activity in a mammal by administering a specific zvegf3 antibody.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
January 27, 2003